

### **Remarks**

Claims 1-2, 4-21, 31, 35-45, 47, 49 and 75-83 are pending in the application and have been rejected. Reconsideration of the rejection is requested.

### **Rejections under 35 U.S.C. Section 112**

Claims 4 and 8 have been amended to correct dependency, as requested by the examiner.

Claim 4 has also been amended to clarify the language of the claim. The amendment does not change the scope of the claim, it clearly overcomes the Section 112 rejection, and entry of the amendment will simplify issues for appeal.

Claims 76 and 79-83 were rejected under Section 112, first paragraph, because the claims were said to contain subject matter that was not described in the specification. In support of the rejection, the Office action cited a portion of the specification on page 35, lines 3-9, that disclosed a conjugate-tracer solution was applied to the pad of a mobilization zone in four lines and dried.

Claim 76 has been amended to clarify that the detectable tracer has been applied to the mobilization zone of the bibulous substrate as a liquid and dried. This amendment more closely parallels the language of the specification and is believed to address the examiner's concern that the "detectable tracer comprises a dried liquid" is not present in the specification. See also the specification at page 16, lines 13-14 ("the analyte-tracer conjugate is dried in mobilization zone 54"). This statement on page 16 of the specification makes it clear to one of skill in the art that applicant was in possession of the invention at the time the application was filed. However, the examiner is reminded that *in ipsius verbis* support for the language of the claim is an inappropriate standard to apply. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsius verbis* [i.e., "in the same words"] to be sufficient").

Claim 77 has also been amended to adopt the language suggested by the examiner that the sample application zone pad "covers the mobilization zone" as described at page 24, line 12 of the specification.

Claim 79 has been amended to state that the test strip comprises multiple lines having

detectable tracer. This language parallels more closely the language cited by the examiner at pages 35-36.

The remaining claims depend from allowable claims, and are allowable for that reason as well as for the specific structure and steps recited in the remaining claims.

These amendments do not raise new issues of patentability, but only clarify the language of the claims by adopting suggestions made by the examiner. These amendments overcome the rejections raised by the examiner, and should be entered to simplify issues for appeal.

### **Rejection under 35 U.S.C. Section 103**

Claims 1, 2, 4, 5-10, 12, 13, 20, 21, 31, 35-36, 40-41, 45, 49 and 75 were rejected as obvious over Boehringer et al. (WO98/39657) in view of Attridge (U.S. 5,631,170). Boehringer was said to show the lateral flow test strip for performing a competitive assay, except for a delayed release agent in the mobilization zone. Attridge was said to remedy this deficiency by disclosing that delayed release agents could be added to the mobilization zone in a competitive assay. To support this rejection, the Office action alleges that both Boehringer et al. and Attridge disclose competitive immunoassays, and that Attridge teaches that delayed release agents provide an opportunity to measure a reference signal and provide a more accurate reference signal. The rejection is unsupported by the evidence, and reconsideration is rejected.

The Attridge waveguide device is a capillary fill biosensor in which two glass plates define a cavity through which a liquid passes (column 5, lines 38-42). The plates are solid plates (column 6, lines 20-22). Fluorescent reagents are placed on the surface of one of the solid plates (column 3, lines 1-11 and lines 27-28) so that the fluorescent reagents can be released into the liquid as the liquid sample passes between the solid plates (column 6, lines 15-30). One of the solid glass plates acts as an optical wave guide that measures an initial fluorescent signal of liquid introduced into the cavity between the plates (a reference signal); that initial signal is then compared to a fluorescent signal obtained after the liquid interacts with a fluorescently labeled antigen analog. Attridge teaches that the fluorescent agents on the surface of the glass plate can be capped with a "capping layer" to delay dissolution of the reagent into the liquid for a few seconds after the introduction of liquid into the

cavity between the plates. The delay in the release of the fluorescent reagent into the liquid in the cavity permits an initial reference fluorescent signal from the liquid to be detected prior to the release of the fluorescent reagent.

The Office action provides a legally inadequate rationale for combining Boehringer et al. and Attridge, namely that Attridge “teaches that delayed release reagents provide for an ideal opportunity to measure a reference signal and provides for more accurate referencing” (Office action at page 7). Since neither Boehringer et al. or the claimed invention is measuring a reference signal prior to release of a fluorescent reagent, Attridge provides no motivation to make the combination proposed by the Office action. Attridge only teaches that the release of fluorescent reagents into the liquid filled cavity between solid wave guide plates allows the initial inherent fluorescent properties of the liquid to be measured. Boehringer et al. uses a completely different system, namely a porous lateral flow test strip in which reagents flow along the test strip instead of into a liquid filled cavity between two solid plates. Boehringer et al. has no need to measure a reference fluorescent signal before the release of fluorescent reagents from the surface of the test strip into a liquid cavity, so one skilled in the art would not have a motivation to add the delayed release cap on top of a fluorescent conjugate in Boehringer et al..

The Office action inappropriately dismissed this argument as the applicant attempting to incorporate the wave guide into the Boehringer device, but that misses the point of the argument. Any obviousness rejection must be supported by a logical rationale for the proposed combination, and the rationale proposed by the Office action is not rational. An actual person of skill in the art would find no motivation to incorporate a delayed release agent in Boehringer (as urged by the Office action) because Boehringer et al. is not measuring a reference fluorescence signal. Since the reason for providing the delayed release reagent in Attridge (allowing measurement of a reference signal before release of the fluorescent agent changes the fluorescence) simply does not exist in Boehringer, one skilled in the art would not be motivated to make the combination. The Office action has simply taken an element in isolation (the delayed release cap in Attridge) and combined it with the very different lateral flow test strip of Boehringer et al., while ignoring the context of the very different assays that render the combination nonobvious.

The proposed combination is also contrary to the examination guidelines recently provided in

MPEP 2143. Those guidelines require (in MPEP 2143A) that for a combination of prior art elements “each element merely performs the same function as it does separately.” The delayed release agent in Attridge would perform a very different function in Boehringer than it does in Attridge. The cap in Attridge slows the release of a fluorescent agent from a glass plate into liquid in the wave guide cavity to permit a fluorescent signal to be measured before the fluorescent signal is released from the surface of the plate. This is a very different function than a delayed release agent would perform in the lateral flow assay of Boehringer, in which no agent is released into liquid in a cavity, and no reference signal is measured before release of a fluorescent agent. The combination proposed by the Office action is therefore impermissible; the proposed combination would change the respective functions of the elements in violation of MPEP 2143(A). The rejection improperly focuses on a disembodied function (delayed release) while disregarding the very different function the cap performs in the Attridge wave guide biosensor. The rejection disregards the invention as a whole, and instead focuses on whether differences themselves would have been obvious, which is contrary to MPEP 2141.02(I).

The proposed combination of Boehringer et al. and Attridge is also contrary to the teachings of the primary Boehringer et al. reference. Boehringer repeatedly expresses a preference for non-bibulous flow through the capture zones. See Boehringer’s abstract, fifth line (“capture zones are disposed on a non-bibulous matrix”); page 24, lines 27-28 (“The matrix is preferably a blocked nitrocellulose capable of non-bibulous flow”); and page 31, lines 15-24 which defines bibulous flow as components carried at substantially equal rates through the matrix. As noted in a prior response, all the examples of the Boehringer et al. application use a matrix that is blocked by methylated-BSA to render the matrix non-bibulous in use (which would avoid delaying the migration of the tracer). See page 32, lines 23-28; page 38, lines 2-4 and 15-16; page 55, line 11; and page 58, lines 34-35. It is not obvious to combine the references to produce delayed release of the tracer in disregard of the repeated teaching of Boehringer et al. that non-bibulous flow is preferred in which the tracer and analyte would move together through the matrix. Although Boehringer does state that the matrix can be capable of non-bibulous flow (page 10, lines 20-24 and page 31, lines 15-16) this does not mean that the Boehringer assay is to be performed under bibulous conditions. The matrix that is “capable of non-bibulous flow” is never used in an assay for non-bibulous flow, since in every instance it is treated by blocking agents that eliminate the bibulous capacity of the matrix. A matrix that is “capable of bibulous flow” is not the same as a lateral flow assay in which bibulous flow occurs; Boehringer et al. eliminates bibulous

flow in the assays. In any event, Boehringer et al. should not be modified contrary to its stated preference for non-bibulous flow by altering it to delay release of the tracer.

Even if the impermissible combination of elements from the references were made, the resulting combination does not disclose all the elements of claim 1. Attridge suggests placing a delayed release cap on top of a fluorescent reagent. Claim 1 calls for the mobilization zone to comprise “a porous material to which the detectable tracer has been applied in the presence of a delayed release agent so that the analyte migrates through the porous material of the bibulous substrate ahead of the detectable tracer.” The Office action at page 7 acknowledges that the patentability of the product is determined by the product based on the product made by the method. The claimed test strip defines a product in which a delayed release agent is incorporated into the porous material to which it is applied, and then migrates *through* the porous material. Since Attridge only discloses placing a cap of delayed release material on top of an impermeable glass plate to release the material into liquid flowing through a chamber above the plate, the combination of Attridge and Boehringer et al. would produce a substrate with a cap of delayed release agent on top of a substrate. Attridge does not suggest incorporating a delayed reagent into a bibulous substrate so that it flows through the porous material.

The Office action attempts to rebut the deficiencies of the rejection by asserting (at page 17) that Attridge is only relied upon for the teaching “that it is known in the art to include delayed release agents in lateral flow assays such as test strips.” However, claim 1 is not directly broadly to incorporating a delayed release agent into a test strip, as alleged. The Office action has disregarded the structural limitations defined by claim 1 in which the detectable tracer is applied to the porous material in the presence of the delayed release agent that allows it to flow “through the porous material” as claimed. The Office action disregards multiple structural limitations of the claim to arrive at the rejection. A prima facie case of obviousness has therefore not been made.

The Examiner is also reminded that none of the cited references disclose or suggest differential flow in which the tracer separates from the analyte and moves behind it to a primary capture zone. Prior Office actions have taken the position that delayed movement of the tracer behind the analyte would be inherent in Boehringer et al., even though the Office has acknowledged (in an October 18, 2005 advisory action) that delayed movement of the tracer is not necessarily present in Boehringer et al. (which is in contravention of the requirements for inherency set forth in MPEP 2112.4 and cases

cited therein). See also the May 15, 2005 Declaration of Buck which provides experimental evidence that Boehringer et al. does not inherently anticipate the claims. In addition, a prima facie case of obviousness can not be predicated on what is not known at the time an invention is made, even if inherency of a certain feature is later established. See MPEP 2141.02 and cases cited therein. Hence a prima facie case of obviousness can not be made based on an alleged inherency of differential flow in Boehringer et al.; the primary reference provides no motivation to delay release of the tracer. There is no teaching in any of the references that delaying the flow of a tracer relative to an analyte in a lateral flow assay is desirable or even happens at all.

Claim 2 further illustrates the deficiencies of the rejection, because Attridge does not suggest a detectable tracer present in a test strip in a position that selectively delays migration of the tracer through the bibulous substrate. At best, Attridge discloses placing a delayed release agent on top of a glass plate so that the tracer is released into liquid passing through cavity of the wave guide biosensor. The proposed combination does not yield the claimed invention because Attridge does not in any way suggest selectively delaying migration of the tracer through the bibulous substrate; Attridge only suggests delaying release of a tracer from the surface of a glass plate into a liquid cavity formed in part by the glass plate.

Claims 6, 11 and 47 were rejected as unpatentable over Boehringer et al. and Attridge, further in view of Fredrickson (U.S. 6,001,658). The Office action acknowledged that Boehringer et al. and Attridge failed to teach that the bibulous liquid collection member contains the mobilization zone as well as the primary and secondary capture areas, or that the detectable tracer is positioned beneath the surface of the test strip. Fredrickson is alleged to cure these deficiencies.

However, Fredrickson only discloses a test strip in which a separate conjugate pad 3 is layered over a membrane 9, so that liquid applied to sample pad 2 can migrate through the sample pad into the layered conjugate pad 3, then along membrane 9 to a test area. The cited reference does not cure the deficiencies of the primary references with respect to claim 6 because the combined references fail to disclose “an analyte analog that has been applied as a liquid to the mobilization zone where it has dried beneath the surface of the test strip along which the liquid sample migrates.” Fredrickson does not show an analyte analog applied as a liquid that has dried beneath the surface of the test strip. The claim is limited by the process steps, which clearly would not produce a separate pad 3 layered on top

of the test strip below a sample application pad. The claimed process steps would produce a detectable tracer that is absorbed into the pores of the collection member; that is not what Fredrickson discloses and a prima facie case of obviousness has not been made.

In addition, it would not be obvious to combine the teachings of Attridge with Fredrickson, because Attridge teaches that a tracer on top of a plate and covered by a delayed release cap for release of the tracer into liquid that flows over the plate through the biosensor cavity. One skilled in the art would not combine the teaching of Attridge with that of Fredrickson in which a conjugate pad 3 is placed beneath a sample application pad 2. Placing the sample application pad 2 over the conjugate pad 3 would interfere with the function of the Attridge assay, in which a tracer is to be released transversely from the solid surface of the biosensor into the liquid passing through the biosensor cavity above the plate. A prima facie case of obviousness is not established when a proposed combination of references would frustrate the purpose or interfere with the function of one of the references, or when there would be a change in the respective functions of the elements when the combination is made. The Attridge cap would clearly function differently in the Boehringer et al. lateral flow assay, because the cap would not slow the release of a tracer into liquid flowing through a cavity above tracer. Claim 6 is therefore allowable.

The Office action also alleges that it would be obvious to combine Boehringer et al. and Fredrickson because “Fredrickson teaches that the membrane is specifically designed for lateral flow in test strips and also provides for a test strip with rapid, volume, timing and temperature independent visually read test strip.” Such a vague, non-specific and generic allegation falls far short of the clear articulation of reasons required by MPEP 2143 to support a prima facie case of obviousness. The generic rationalization provided in the Office action does not explain why one skilled in the art would have specifically modified Boehringer by layering the conjugate pad of Fredrickson on top of the test strip, using a delayed release capping agent from Attridge on top of the conjugate, then modifying that combination by moving the conjugate out of the Fredrickson conjugate pad and into the porous test strip. There is no rationale for such a convoluted series of modifications, and the elements as combined would have different functions than in the cited references. Moreover, even if the combination were made, it would not produce the claimed invention without the further modification of moving the conjugate from Fredrickson’s conjugate pad and into the porous strip. There is no prima

facie case of obviousness with respect to claims 6, 11 and 47.

Claim 7 is rejected as obvious over the combination of Boehringer et al. and Attridge in view of Leuving. Leuving is said to disclose tracer particles that carry a charge, have a size that is similar to the particles disclosed in applicants' specification (page 21), and can be used in detection methods. The Office action alleges that claim 7 is obvious because Boehringer et al., Attridge and Leuving disclose the same devices and reagents as recited in the instant claims, so that one of ordinary skill in the art would expect the detectable tracer to have a retarded migration rate relative to the migration of the analyte and to also possess a polarity or charge that interacts with the bibulous substrate. However, there is no disclosure in any of the references that the tracer has a polarity or charge that interacts with the bibulous substrate to retard migration of the tracer relative to migration of the analyte. The Office action appears to conclude that some random combination of variables in the cited references could inherently produce such an interaction, which would render the combination obvious because some of the devices and reagents are similar. Such random possible combinations do not establish a prima facie case of obviousness and the rejection is overcome. In particular, the proposed rejection violates the requirement of the examination guidelines in MPEP 2142 and 2143 that a clear articulation be given of the reasons the claimed invention would be obvious. There is no rational underpinning to support the specific legal conclusions of obviousness as required by *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) as cited in MPEP 2142.

Claim 76 has not been rejected in view of the prior art, and is allowable as amended to overcome the Section 112 rejection.

Claim 77 is rejected as obvious over the combination of Boehringer et al. and Attridge in view of Ledden et al. (U.S. 6,093,546). It would not be obvious to include Attridge in any combination of references that would result in the mobilization zone being covered. Attridge teaches that the tracer is to be released from the surface of a solid plate into liquid that passes through the wave guide liquid chamber. No person of skill in the art would consider combining Attridge with any reference (such as Ledden et al.) that proposes to cover the tracer. It would defeat and frustrate the function of Attridge to cover the tracer (and delayed release agent) that Attridge is cited as disclosing with a pad that would interfere with its function of releasing the tracer from the plate into the liquid that passes through the wave guide. Claim 78 is allowable for similar reasons.



Claim 79 is free of the cited prior art, and is allowable as amended to overcome the Section 112 rejection.

The Office action asserts that applicant is attempting to incorporate the wave guide of Attridge into Boehringer et al., whereas the examiner only wants to take the delayed release agent out of context from Attridge and import it into Boehringer et al. Applicants submit that the Attridge reference must be considered in the context of the invention it discloses and the specific motivation it provides, and not merely as a collection of disembodied parts that can be incorporated randomly into the device of Boehringer et al. A prima facie case of obviousness can not be established in disregard of the actual functions elements are performing in the cited references. To provide a fair rationale for a combination of references requires more than a generic observation that the devices are similar and details from each could possibly be combined in a manner that produces the claimed invention.

It is believed that the claims are now in condition for allowance. If any matters remain for discussion before a Notice of Allowance is issued, the examiner is invited to telephone the undersigned patent attorney at the telephone number shown in the signature line below.

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